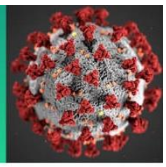
COVID-19 Science Update



From the Office of the Chief Medical Officer, CDC COVID-19 Response, and the CDC Library, Atlanta, GA.
Intended for use by public health professionals responding to the COVID-19 pandemic.

***** Available on-line at https://www.cdc.gov/library/covid19 *****

Section headings in the COVID-19 Science Update align with the CDC Science Agenda for COVID-19.

Prevention, Mitigation and Intervention Strategies

PEER-REVIEWED

Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data. Shaw *et al*. Lancet (May 12, 2021).

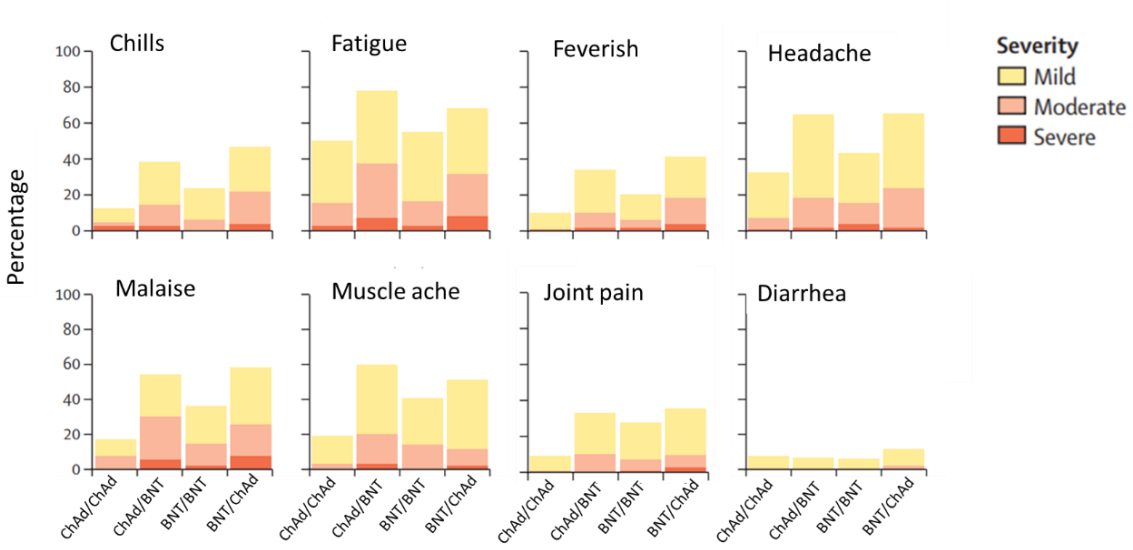
Key findings:

- Participants receiving 2 doses of different vaccines reported more systemic symptoms (e.g., chills, fatigue, feverishness, headache, malaise) than those who received 2 doses of the same vaccine (Figure).
    - Symptoms were short lived (generally ≤48 hours); none required hospitalization due to symptoms.

Methods: Interim analysis from a UK multi-site, randomized trial comparing timing and safety of mixed COVID-19 vaccine schedules (Oxford/AstraZeneca ChAdOx1 vaccine and Pfizer/BioNTech BNT162b2 vaccine followed 28 days later with the other vaccine) among 461 participants (age ≥50 years), February 2021. Frequency and severity of systemic symptoms after vaccination were identified. *Limitations*: Initial safety data in small study; restricted to older adults.

Implications: Mixing adenovirus-based and mRNA-based COVID-19 vaccines increased non-severe systemic symptoms.

Figure:



Note: Adapted from Shaw *et al*. Self-reported severity of systemic symptoms within 7 days of 2nd dose, graded as **mild** (easily tolerated; no activity limitation), **moderate** (some daily activity limitation), or **severe** (unable to perform normal daily activity) by vaccination schedule. ChAd: Oxford/AstraZeneca ChAdOx1; BNT: Pfizer/BioNTech BNT162b2. Reprinted from The Lancet, Shaw et al., Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data, Copyright 2021, with permission from Elsevier.

Immunogenicity of COVID-19 mRNA vaccines in pregnant and lactating women. Collier *et al.* JAMA (May 13, 2021).

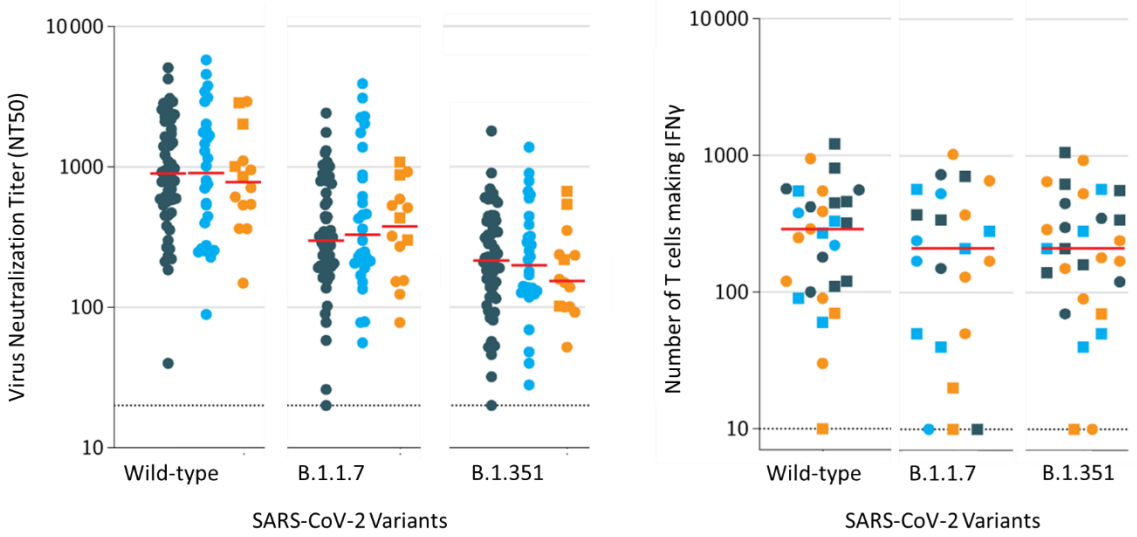
Key findings:

- mRNA vaccines induced similar levels of B cell (antibody) and T cell responses in pregnant, lactating, and non-pregnant women (Figure).
    - Neutralizing antibody titers against the SARS-CoV-2 B.1.1.7 and B.1.351 variants were reduced in all groups, but T-cell responses were preserved (Figure).
- Binding and neutralizing antibodies were also found in infant cord blood and breast milk following vaccination of pregnant and lactating women.

Methods: Exploratory, prospective cohort study measuring T cell and B cell responses in pregnant (n = 30), lactating (n = 16), or non-pregnant/non-lactating (n = 57) women who received an mRNA vaccine between December 2020 and March 2021 and unvaccinated women (22 pregnant and 6 non-pregnant) who had confirmed SARS-CoV-2 infection between April 2020 and March 2021. *Limitations:* Small convenience sample.

Implications: Pregnant and lactating women have strong immune responses to mRNA vaccines that also recognize known SARS-CoV-2 variants.

Figure:



Note: Adapted from Collier *et al*. Neutralizing antibody titers (NT50, left) and T cell responses (spot-forming cells producing interferon-gamma [IFNγ] to SARS-CoV-2 spike protein, right), 2 through 8 weeks after second COVID-19 vaccination dose among **non-pregnant**, **pregnant**, and **lactating** women. The red bars indicate the median response and the dotted lines represent the limit of detection. Squares represent Moderna mRNA-1273-vaccinated women and circles represent Pfizer/BioNTech BNT162b2-vaccinated women. Reproduced with permission from JAMA, 2021. Published online May 13, 2021. https://doi.org/10.1001/jama.2021.7563.

Covid-19 vaccine acceptance in California state prisons. Chin *et al.* NEJM (May 12, 2021).

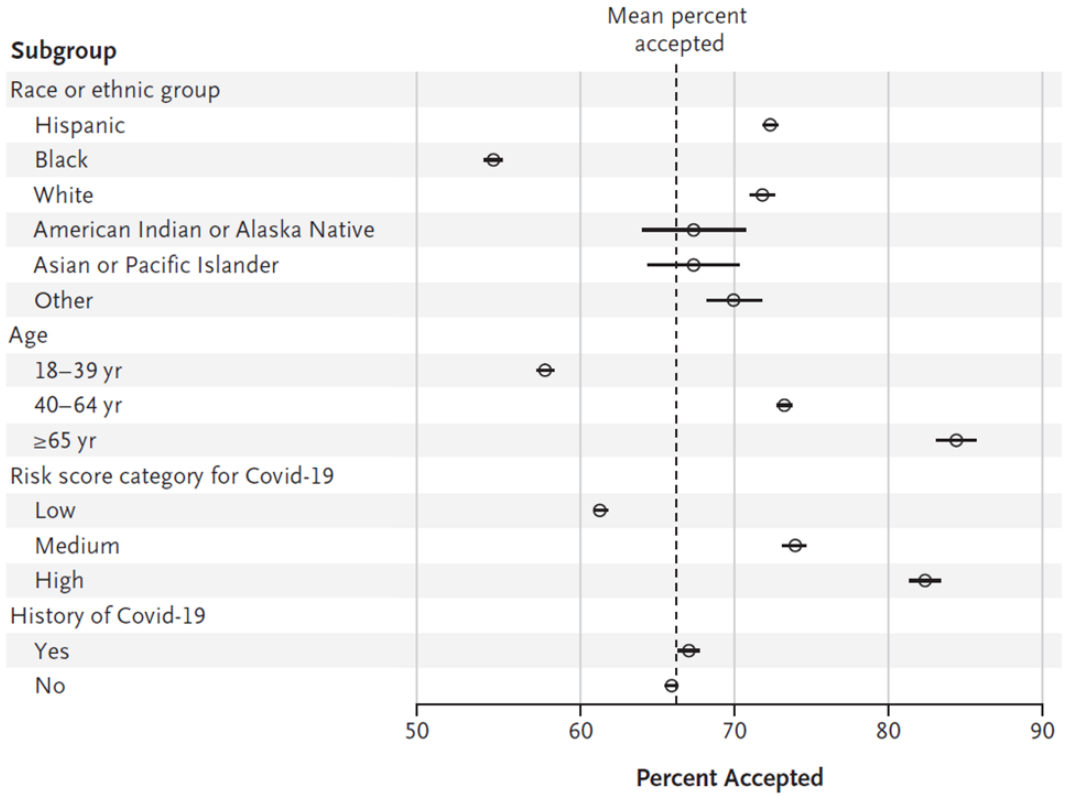
Key findings:

- Among incarcerated adults in California who were offered vaccine, 66.5% accepted at least 1 dose.
- Vaccine acceptance was:
  - Lowest among non-Hispanic Blacks (54.9%; 99.6% CI 54.3%-55.5%) (Figure).
  - Lower among younger and healthier residents (those with a low risk score) than older and medically vulnerable residents (those with a high risk score) (Figure).
- Among those who initially declined vaccination, 45.9% accepted when re-offered.

Methods: California Department of Corrections and Rehabilitation (CDCR) records for 64,633 prisoners offered COVID-19 vaccination between December 22, 2020 and March 4, 2021. Predicted margins estimated from logistic regression models adjusted for prison, prisoner security level, room type, labor participation, race/ethnicity, COVID-19 history, age, and CDCR COVID-19 risk score group. Risk score for potential severity of infection was based on age and 16 health conditions. *Limitations*: Results do not include information on receipt of second dose; COVID-19 history prior to incarceration not considered.

Implications: Attitudes towards vaccination may change over time, so providing another opportunity for vaccination to those who decline initially may increase vaccinations.

Figure:



Note: Adapted from Chin *et al*. Adjusted percent of prisoners offered vaccine who accepted. All race/ethnicity categories other than Hispanic are non-Hispanic. Low risk score: age <65 years and 0–1 comorbidity; medium risk score: age <65 years and 2–3 comorbidities; high risk score: age ≥65 years and/or ≥4 comorbidities. History of COVID-19 is a positive test while in CDCR custody before a vaccine offer. From the New England Journal of Medicine, Chin et al., COVID-19 vaccine acceptance in California state prisons. May 12, 2021, online ahead of print. Copyright © 2021 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Public attitudes toward COVID-19 vaccination: The role of vaccine attributes, incentives, and misinformation. Kreps *et al.* Nature Partner Journals Vaccines (May 14, 2021).

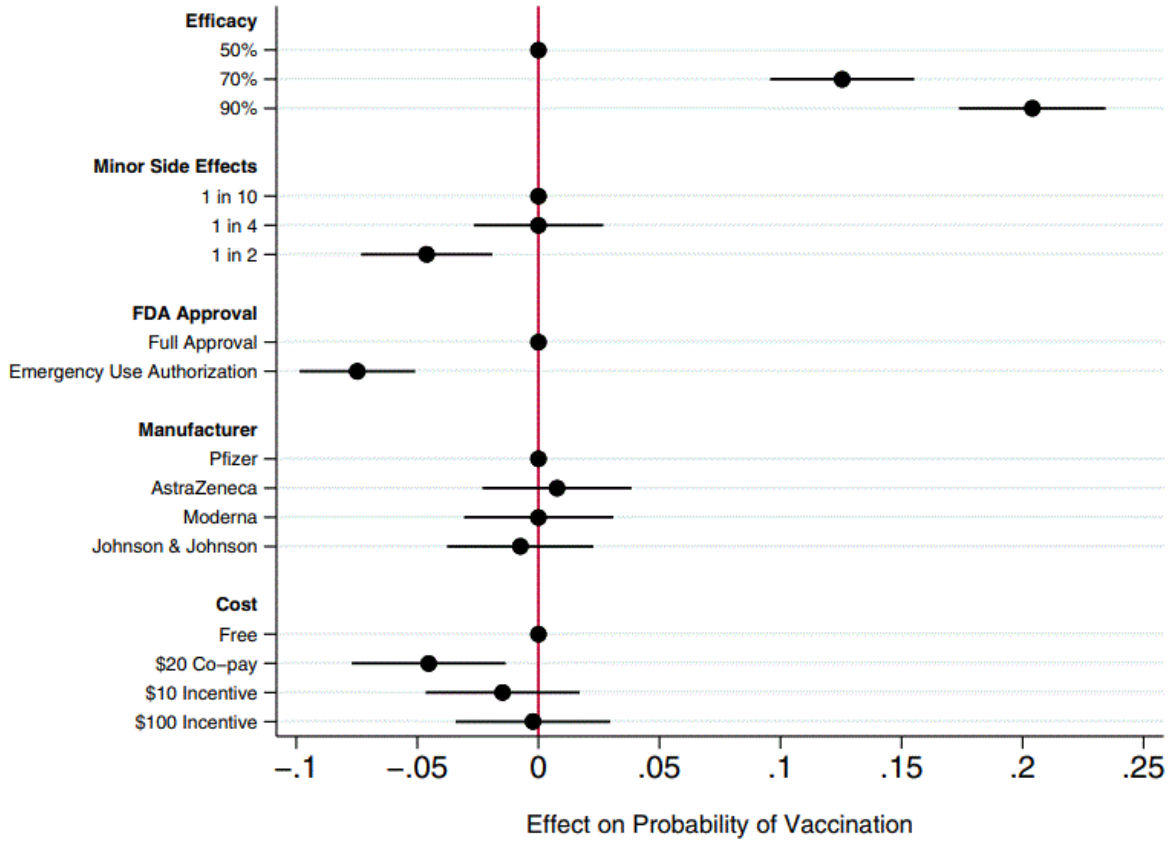
Key findings:

- Prior to vaccine approval, US adults' willingness to receive COVID-19 vaccine was positively associated with efficacy and negatively associated with cost (co-pay), vaccine approval status and incidence of minor side effects (Figure).
- Willingness to receive a COVID-19 vaccine was not associated with financial incentive and brand (Figure).
- Belief in COVID-19 misinformation was high but did not affect vaccine willingness to receive a vaccine.

Methods: Survey of 1,096 adults on the Lucid platform, matched to the demographics of the US population on age, gender, ethnicity, and geographic region, October 29–30, 2020. A misinformation index captured the extent to which each subject believes or rejects 8 claims (5 false; 3 true) about COVID-19 treatments. *Limitations*: Convenience sample conducted prior to FDA emergency use authorization and availability of data on vaccine effectiveness.

Implications: Emphasizing the high efficacy of COVID vaccines, that they are free, and that side effects are generally mild might increase uptake.

Figure:



Note: Adapted from Kreps *et al*. Circles show estimated effects of vaccine attributes on probability of vaccination; horizontal bars are 95% CIs. Circles without bars show baseline for each attribute. Licensed under CC BY 4.0.

PREPRINTS (NOT PEER-REVIEWED)

Plans to vaccinate children for COVID-19: a survey of US parents. Teasdale *et al.* medRxiv (May 13, 2021). **Published in The Journal of Pediatrics (October, 2021).**

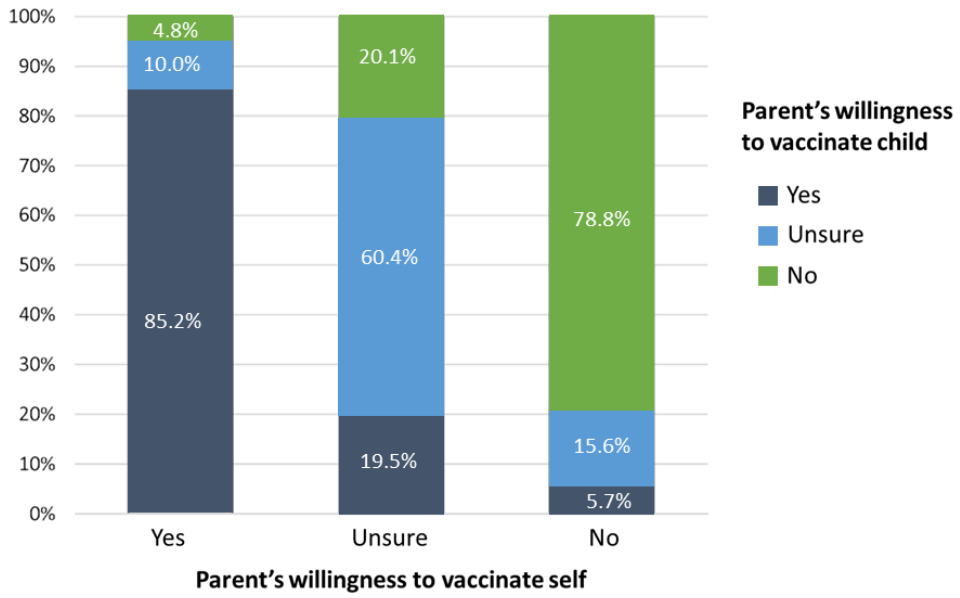
Key findings:

- Only half of US parents (49.4%) reported plans to have their youngest child receive a COVID-19 vaccine:
  - Of these parents, 78.2% had concerns about safety and effectiveness and 23.0% perceived lack of need.
  - A parent's willingness to be vaccine their child strongly correlated with their willingness to be vaccinated themselves (Figure).
  - Parents with lower likelihood of vaccinating their child were female (adjusted prevalence ratio [aPR]: 0.69, 95% CI 0.62-0.77), high school educated or less (aPR: 0.73; 95% CI 0.62-0.86), and lower income (household income of <$25,000, aPR: 0.75, 95% CI 0.64-0.88).

Methods: Community-based, non-probability online survey of 2,047 parents/caregivers >18 years old of children <12 years of age, as of March 2021. Poisson regression models were fitted to estimate prevalence ratios (adjusted for demographic and household characteristics) that compared parents planning and not planning to vaccinate. *Limitations:* Did not include data on adolescents; excluded parents without access to the internet.

Implications: Focused outreach and educational efforts might be required to reach child vaccination levels needed to curb viral transmission.

Figure:



Note: Adapted from Teasdale *et al*. Parental intentions to vaccinate children against COVID-19 according to parents' own vaccination status in the US, March 9–April 2, 2021. Licensed under CC-BY-NC-ND 4.0.

Detection, Burden, and Impact

PEER-REVIEWED

Post-acute effects of SARS-CoV-2 infection in individuals not requiring hospital admission: a Danish population-based cohort study. Lund *et al*. Lancet Infectious Diseases (May 10, 2021).

Key findings:

- Compared to SARS-CoV-2-negative persons, 2 weeks to 6 months after infection, SARS-CoV-2-positive individuals who initially did not require hospitalization would more often:
  - Receive a hospital diagnosis of venous thromboembolism (aRR 1.77, 95% CI 1.09-2.86) or dyspnea (aRR 2.00, 95% CI 1.62-2.48).
  - Initiate short-acting β2-agonist bronchodilator therapy (aRR 1.32, 95% CI 1.09-1.60).
  - Visit general practitioners (aRR 1.18, 95% CI 1.15-1.22) and outpatient hospital clinics (aRR 1.10, 95% CI 1.05-1.16).
- There was no increased risk of diagnoses other than venous thromboembolism and dyspnea.

Methods: Population-based cohort study used Danish prescription, patient, and health insurance registries to match SARS-CoV-2-positive individuals (n = 8,983) to a SARS-CoV-2-negative reference population (n = 80,894), February 27 to May 31, 2020. Study outcomes were delayed acute complications, chronic disease, hospital visits due to persisting symptoms, and prescription drug use. *Limitations*: Follow-up period was only 6 months.

Implications: Risk of severe delayed complications after SARS-CoV-2 infection that did not require hospitalization is low.

PREPRINTS (NOT PEER-REVIEWED)

Feasibility and acceptability of community COVID-19 testing strategies (FACTS) in a university setting. Hirst *et al.* SSRN (May 10, 2021). **Published in Open Forum Infectious Diseases as Feasibility and acceptability of community coronavirus disease 2019 testing strategies (FACTS) in a university setting (October 4, 2021).**

Key findings:

- 2,728 SARS-CoV-2 antigen self-test results were performed, with a mean of 5.0 ± 3.0 tests administered per participant.
    - 9 results from 8 participants were positive, 3 of which were later determined to be false positives by confirmatory RT-PCR.
- Participants reported that self-testing was beneficial for them (97%), their friends and family (99.5%), people they live with (98%), and their wider community (98.5%).

Methods: Mixed methods cohort study (N = 551, 25% of those invited) that involved self-administered testing (lateral flow assay), survey questionnaires (n = 214), and interviews (n = 18). Participants were adults working or studying at 3 main sites at the University of Oxford. Testing data were collected with a smartphone app from December 2020 to January 2021. *Limitations:* Low overall and questionnaire response rates; a few positive results were not verifiable due to poor smartphone photographs.

Implications: Self-testing was acceptable, and people could accurately interpret results.

Infection and vaccine-induced neutralizing antibody responses to the SARS-CoV-2 B.1.617.1 variant. Edara *et al.* bioRxiv (May 10, 2021). **Published in NEJM as Infection and vaccine-induced neutralizing-antibody responses to the SARS-CoV-2 B.1.617 variants (August 12, 2021).**

Key findings:

- Sera from 100% of persons vaccinated with mRNA vaccines were able to neutralize the B.1.617.1 SARS-CoV-2 variant.
    - Compared with wild-type (WA1) SARS-CoV-2, B.617.1 was 6.5–7-fold less susceptible to neutralization by sera from convalescent and vaccinated individuals (Figure).
- Most sera (19/24) from convalescent patients were able to neutralize the B.1.617.1 variant (Figure).

Methods: A live virus neutralization test was used to compare the titer of neutralizing antibody to wild-type (WA1) SARS-CoV-2 and the B.1.617.1 variant in sera from three cohorts: individuals 31–91 days after COVID-19 symptom onset (n = 24), Moderna mRNA-1273-vaccinated individuals (35–51 days post-2nd dose, n = 15), and Pfizer/BioNTech BNT162b2-vaccinated individuals (7–27 days post-2nd dose, n = 10). *Limitation:* Small sample sizes within each cohort.

Implications: The Moderna mRNA-1273 and Pfizer/BioNTech BNT162b2 mRNA vaccines likely provide protective immunity against the B.1.617.1 variant, which has spread rapidly throughout India and to several other countries.

Natural History of SARS-CoV-2 Infection

PEER-REVIEWED

A retrospective cohort study of 12,306 pediatric COVID-19 patients in the United States. Parcha *et al*. Scientific Reports (May 13, 2021).

Key findings:

- 672 of 12,306 children and adolescents with COVID-19 required hospitalization.
  - 17.6% required critical care and 4.1% required mechanical ventilation.
  - There were ≤10 deaths.
  - Fever, gastrointestinal, and respiratory symptoms were more common in hospitalized compared to non-hospitalized children and adolescents.
  - Risk of hospitalization was greater in non-Hispanic Black (RR 1.97, 95% CI 1.49-2.61) and Hispanic (RR 1.31, 95% CI 1.03-1.78) children and adolescents compared with non-Hispanic White children and adolescents.

Methods: Retrospective cohort study of clinical characteristics and outcomes among youth in the US (age <18 years) with PCR-confirmed SARS-CoV-2 infection between April 1 and October 31, 2020. Data were collected from a national healthcare system electronic database, stratified by hospitalization status, and propensity-score matched by sex and race/ethnicity. Categories with fewer than 10 entries were obscured for privacy reasons. *Limitations*: Incompleteness of health records; variable health system testing indications; some hospitalizations may have been due to causes other than COVID-19.

Implications: While children and adolescents hospitalized with COVID-19 rarely had severe outcomes, there were racial/ethnic disparities in risk of hospitalization.

In Brief

Detection, Burden, and Impact

- Taquet *et al*. **Cerebral venous thrombosis and portal vein thrombosis: a retrospective cohort study of 537,913 COVID-19 cases.** medRxiv (Preprint; May 11, 2021). **Published in eClinicalMedicine (July 31, 2021).** COVID-19 patients had a significantly higher two-week risk of being diagnosed with a cerebral venous thrombosis (CVT) or portal vein thrombosis (PVT) compared with matched cohorts diagnosed with influenza (n = 392,424 in each cohort; RR = 3.83, 95% CI 1.56-9.41 for CVT; RR = 1.39, 95% CI 1.06-1.83 for PVT), or receiving an mRNA vaccine (n = 366,869 in each cohort; RR = 6.67, 95% CI 1.98-22.43 for CVT; RR = 7.40, 95% CI 4.87-11.24 for PVT). The incidence of CVT after COVID-19 diagnosis was 42.8 per million people (95% CI 28.5-64.2).

Transmission of SARS-CoV-2

- Marc *et al*. **Quantifying the relationship between SARS-CoV-2 viral load and infectiousness**. medRxiv (Preprint; May 8, 2021). **Published in eLife (September 27, 2021).** Using data collected from a March–April 2020 study of 257 index cases and 574 high-risk contacts with frequent follow-up, models predicted the median probability of household transmission was 15% (range 5%-100%). The probability of household transmission increased to 37% when the viral load was greater than 10 $\log_{10}$ copies per mL.

Natural History of SARS-CoV-2 Infection

- Dispinseri *et al*. **Neutralizing antibody responses to SARS-CoV-2 in symptomatic COVID-19 is persistent and critical for survival.** Nature Communications (May 11, 2021). In a longitudinal cohort of 162 COVID-19 patients, early development of neutralizing antibodies against SARS-CoV-2 correlated with virus control and survival. Neutralizing antibodies and anti-spike IgG persisted in the majority of recovered patients regardless of disease severity for up to 8 months from onset of symptoms.

Prevention, Mitigation, and Intervention Strategies

- Watanabe *et al*. **Central obesity, smoking habit and hypertension are associated with lower antibody titers in response to COVID-19 mRNA vaccine.** Diabetes Metabolism Research and Reviews (May 6, 2021). In 86 healthcare workers in Italy, lower antibody levels were associated with higher waist circumference (R = −0.324, p = 0.004), being a smoker compared with a non-smoker (1099 units [U]/mL vs. 1921 U/mL), having hypertension compared with normal blood pressure (650 U/mL vs 1911 U/mL), or having dyslipidemia compared with normal serum lipid levels (534 U/mL vs 1872 U/mL) following 2 doses of the Pfizer/BioNTech BNT162b2 vaccine.

- Saunders, *et al*. **Neutralizing antibody vaccine for pandemic and pre-emergent coronaviruses.** Nature (May 10, 2021). Immunization of rhesus macaques with SARS-CoV-2 receptor binding domain protein elicited neutralizing antibody responses against SARS-CoV-2 that also neutralized SARS-CoV-2 variants B.1.1.7, P.1, and B.1.351; SARS-CoV-1; and bat coronaviruses.

- Drake *et al*. **Non-steroidal anti-inflammatory drug use and outcomes of COVID-19 in the ISARIC clinical characterization protocol UK cohort: a matched, prospective cohort study.** Lancet Rheumatology (May 7, 2021). In an adjusted propensity score matching analysis (n = 4,205 in each group) using patient data from 255 UK healthcare centers between January 17 and August 10, 2020, people taking non-steroidal anti-inflammatory drugs during the 2 weeks prior to admission did not have poorer in-hospital mortality (p = 0.35) or admission to critical care (p = 0.89).

- Roeker *et al*. **COVID-19 vaccine efficacy in patients with chronic lymphocytic leukemia.** Leukemia (May 13, 2021). Only 23/44 (52.3%) patients with chronic lymphocytic leukemia tested positive for anti-SARS-CoV-2 spike antibodies 21 days following the second dose of an mRNA vaccine.

- Anand *et al*. **Antibody response to COVID-19 vaccination in patients receiving dialysis.** medRxiv (Preprint; May 12, 2021). **Published in Journal of the American Society of Nephrology (October 2021).** Among 610 fully vaccinated dialysis patients, approximately 135 (22.1%) had absent or attenuated antibody responses at least 14 days following vaccination with Moderna mRNA-1273, Pfizer/BioNTech BNT162b2, or Janssen (Johnson & Johnson) Ad26.CoV2.S vaccines.

- Haberman *et al*. **Methotrexate hampers immunogenicity to BNT162b2 mRNA COVID-19 vaccine in immune-mediated inflammatory disease.** medRxiv (Preprint; May 12, 2021). **Published in Annals of the Rheumatic Diseases (May 25, 2021).** In 2 independent cohorts, fewer patients on methotrexate (MTX) for immune-mediated inflammatory disease (IMID) developed antibody responses following 2 doses of the Pfizer/BioNTech BNT162b2 vaccine (28/45, 62.2%) compared with IMID patients receiving other treatments (34/37, 91.9%) or healthy individuals (204/208, 98.1%).

cdc.gov/coronavirus